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Conversion of (−)-3-Dehydroshikimic Acid into Derivatives of the (+)-Enantiomer

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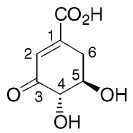
Abstract: (−)-3-DHS (**1**), a compound available in large quantity through "engineering" of the shikimic acid pathway, has been converted over eight steps into the methyl ester, *ent*-**2**, of the (+)-enantiomer. Methyl (+)-shikimate (**15**) and its C-3 epimer (*ent*-**5**) have also been prepared by related means.

Recent developments in "engineering" of the shikimic acid pathway have enabled the high volume production of (−)-3-dehydroshikimic acid [**1**, (−)-3-DHS] from glucose.[1] Indeed, such methodology has been finessed to the extent that Frost and co-workers have identified recombinant strains of *E. coli*. and reaction conditions enabling generation of this fascinating material at levels of 69 g/L of fermentation broth.[2] As such, (−)-3-DHS must now be regarded as an important new chiron that should have manifold uses as a starting material in the chemical synthesis of a wide range of target molecules. The compound has already been employed in the preparation of protocatechuic acid, vanillin, catechol, adipic acid, gallic acid, and pyrogallol.[1,3] However, the chirality embodied within (−)-3-DHS has only been exploited on three occasions. Thus, Wood and Ganem[4] employed this material in the synthesis of (−)-3-homoshikimic acid and its 3-phosphate derivative while Falck and co-workers[5] used enone **1** in the preparation of L-α-phosphatidyl-D-*myo*-inositol 3,4,5-triphosphate, a compound which plays a significant role in intracellular signal transduction. Entwistle and Hudlicky[6] have used the same starting material for the preparation of certain pseudosugars. We are also using compound **1** in the synthesis of novel carbohydrate derivatives.[7] In this and other contexts the utility of (−)-3-DHS as a starting material for chemical synthesis could be greatly enhanced if methods were available for its conversion into the (+)-enantiomer, viz. *ent*-**1**, and/or derivatives thereof. We now detail such methods.



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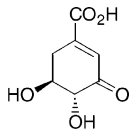
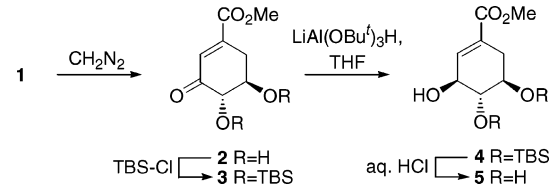


ent-**1**

SCHEME 1



Our initial efforts were focused on direct means for converting (−)-3-DHS into (+)-3-DHS. To these ends, the former compound was subject to various Mitsunobu-type reaction conditions with a variety of *O*-centered nucleophiles but only aromatic products resulting from elimination reactions were observed. These results led us to conclude that achieving the desired "enantiomeric switching" would require we operate, as much as possible, at a lower and, therefore, less sensitive oxidation level, viz. with shikimates rather than dehydroshikimates. This consideration became part of a strategy wherein the C-3 carbonyl within **1** would be reduced to the corresponding β-alcohol, the C-5 hydroxyl oxidized to the corresponding ketone, and the $\Delta^{1,2}$-double bond moved into conjugation with the newly installed "C-5" carbonyl. The early stages of the successful implementation of these ideas are shown in Scheme 1 and involved initial conversion of (−)-3-DHS (**1**) into the corresponding and previously reported[4,5] ester **2** (80%) using diazomethane. The hydroxy groups within the latter compound were then protected as TBS-ethers so as to give compound **3**[4,5] (81%). Stereoselective 1,2-reduction of the enone moiety within product **3** proved rather difficult to achieve and a variety of reagents was investigated before we resorted to Falck's conditions[5] involving lithium tri-*tert*-butoxyaluminohydride and thereby obtained the target allylic alcohol **4**[5] in 82% yield. Proof of the stereochemical outcome of this reduction followed from single-crystal X-ray analysis of a derivative (vide infra). Cleavage of the TBS-ethers within compound **4** was achieved using aqueous hydrochloric acid in ethanol, and in this way, the pivotal methyl (−)-3-*epi*-shikimate **5**[8] was obtained in 84% yield.

An alternate and equally efficient route to compound **5** started from cheap and commercially available quinic acid (**6**). It is based upon modifications of procedures recently reported by Maycock and co-workers,[8b] as outlined in Scheme 2. Thus, reaction of acid **6** with a methanolic solution of 2,2,3,3-tetramethoxybutane (2,2,3,3-TMB) and trimethyl orthoformate in the presence of (+)-camphorsulfonic acid monohydrate [(+)-CSA·H_2O] afforded the acetal ester **7**[9] (82%). The 2°-alcohol moiety associated with this product was oxidized, using the

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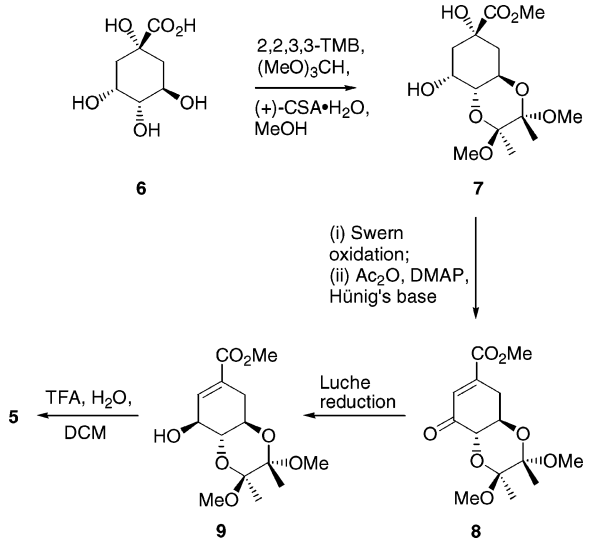
SCHEME 2



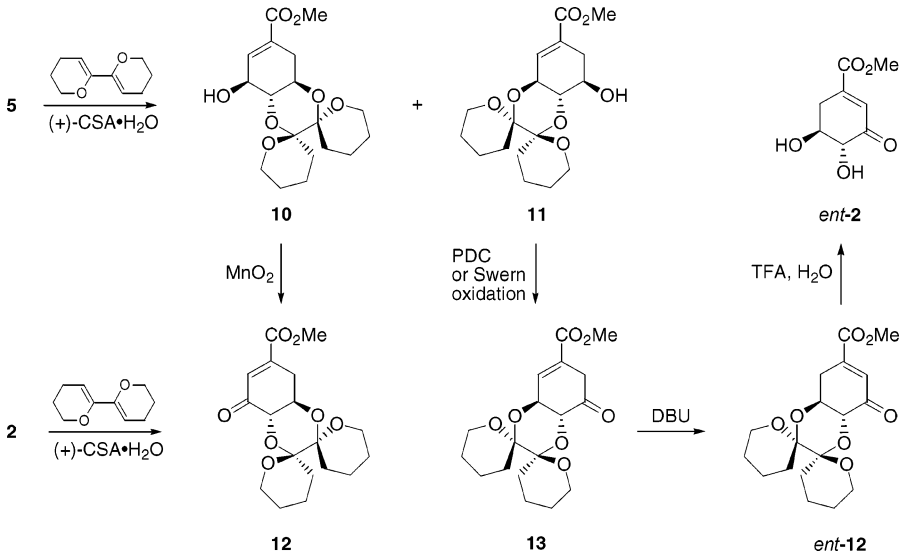
Swern reagent, to the corresponding ketone and the 3°-hydroxyl group acetylated. The resulting β-acetoxy ketone underwent spontaneous elimination of the elements of acetic acid to give the protected 3-DHS derivative **8**[8b] (72% from **6**). Luche reduction[10] of this enone then afforded the 3-*epi*-shikimate derivative **9**[8b] (87%) together with small quantities (7%) of a readily separable isomer presumed to be the shikimate-configured epimer. Cleavage of the bis-acetal protecting group within compound **9** using 5:1 v/v TFA/water at 18 °C[8b] delivered the target compound **5** (94%) which was identical, in all respects, with material obtained by the first route (Scheme 1).

Treatment of the "all-trans" triol **5** with 6,6′-bi(3,4-dihydro-2*H*-pyran)[11] (bis-DHP) in the presence of (+)-CSA·H_2O afforded, as shown in Scheme 3, a ca. 3:1 mixture of the expected regioisomeric dispiroketals **10** and **11** (ca. 80% combined yield)[12] together with small quantities (6%) of an as yet unidentified third isomer. Since the components of this mixture could only be separated from one another by tedious chromatographic methods, it was treated with activated MnO_2[13] in order to selectively oxidize the allylic hydroxyl moiety within the former product to the corresponding conjugated ketone **12** (18% from **5**).

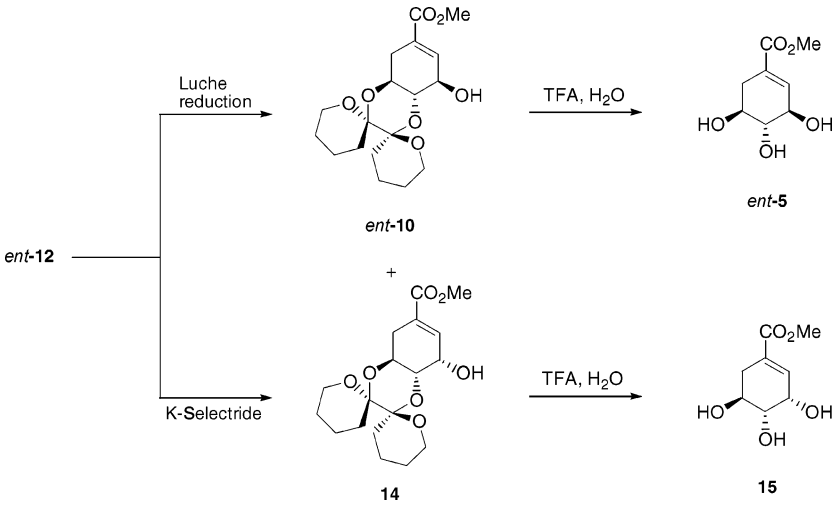
Separation of this ketone (and the unidentified by product) from the desired compound **11** (54% from **5**) was then easily effected by flash chromatography and the structure of the latter confirmed by single-crystal X-ray analysis (see the Supporting Information). The spectral data derived from compound **12** proved identical with those obtained from an authentic sample generated in 79% yield by reaction of compound **2** with bis-DHP under the usual conditions. Oxidation of alcohol **11** to the corresponding ketone **13** could be achieved with PCC,[14] but use of PDC[15] in the presence of 4 Å molecular sieves proved more effective with the target compound thus being obtained in 90% yield. NMR analysis of the oxidation mixture obtained in this manner revealed that it contained ca. 1% of the conjugated isomer *ent*-**12**. The complete conversion of compound **13** into congener *ent*-**12** (95%) was best effected by treating the former with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in chloroform at 0 °C. Alternately, successive treatment of compound **11** with oxalyl chloride/DMSO/Hünig's base then DBU resulted in direct (one-pot) generation of the conjugated enone *ent*-**12** in 77% yield. Compound *ent*-**12** obtained by either means proved identical, as judged by ^{1}H and ^{13}C NMR analyses, with enantiomer **12** while the specific rotations for each were of essentially the same magnitude but opposite sign (see the Supporting Information). Furthermore, cleavage of bis-acetal *ent*-**12** using aqueous trifluoroacetic acid then gave methyl (+)-3-DHS (*ent*-**2**) (60%) which proved identical with compound **2** save for the sign of the specific rotation. In summary, then, the conversion of (−)-3-DHS (**1**) or quinic acid (**6**) into *ent*-**2** was achieved in eight steps, all involving operationally simple procedures, and 13% overall yield. The pivotal part of the sequence, viz. the converstion of compound **5** into enone *ent*-**12**, was achieved in three steps and 46% overall yield.

Compound *ent*-**12** has also proven to be a useful precursor to non-natural shikimic acid derivatives (Scheme 4). Thus, Luche reduction[10] of this enone produced an 84:

SCHEME 3



SCHEME 4



16 mixture of *ent*-**10** and its C3-epimer **14** (92% combined yield) which could be separated from one another by flash chromatography. Selective formation of compound **14** (79%, <3% of *ent*-**10**) could be achieved by reduction of enone *ent*-**12** with K-Selectride. Hydrolysis of each of bis-acetals *ent*-**10** and **14** using 10:1 v/v TFA/water at 18 °C then afforded methyl (+)-3-*epi*-shikimate (*ent*-**5**) (100%) and methyl (+)-shikimate (**15**)[16] (94%), respectively.

The present work provides simple methods for the conversion of abundant (−)-3-DHS (**1**) and (−)-quinic acid (**6**) into derivatives of (+)-3-DHS, (+)-shikimic acid, and (+)-3-*epi*-shikimic acid. As such the synthetic utility of chirons **1** and **6** should be considerably enhanced.

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Supporting Information Available: Experimental procedures for compounds **4**, **5**, *ent*-**5**, and **15**; experimental procedures and characterization for compounds *ent*-**2**, *ent*-**10**, **11**, **12**, *ent*-**12**, **13**, and **14**; crystallography for compound **11**; ^{13}C NMR spectra for compounds *ent*-**2**, *ent*-**10**, *ent*-**12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Reaction of compound **5** with 2,2,3,3-TMB and trimethyl orthoformate in the presence of (+)-CSA·H_2O resulted in a ca. 2:1 mixture of bis-acetal **9** and its regioisomer (77% combined yield). The use of chiral *bis*-DHP derivatives (see, for example: Boons, G.-J.; Entwistle, D. A.; Ley, S. V.; Woods, M. *Tetrahedron Lett.* **1993**, *34*, 5649) to effect more selective conversion of compound **5** into target **11** was not considered because of the likely high cost of producing such protecting agents and the multistep syntheses necessary for their preparation.

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